Facile Deuteration of Chiral *N,N'*-Substituted Piperazines

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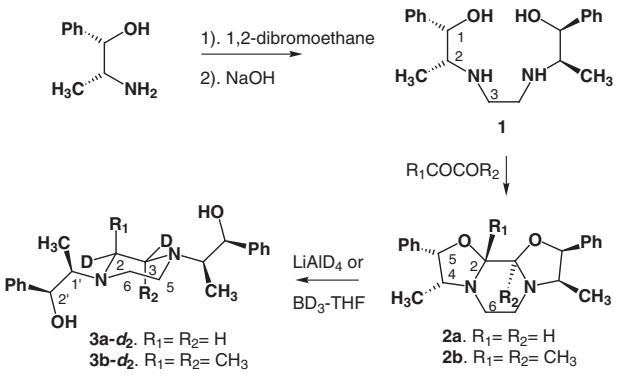
Abstract: The synthesis of four chiral *N,N'*-substituted piperazines stereoselectively labelled with deuterium atoms is described. The preparation was accomplished by reduction of norephedrine derived bisoxazolidines with $LiAlD_4$ or BD_3•THF to afford 2,3-d_2-piperazine and 2,3-dimethyl-2,3-d_2-piperazine, while 2,2,3,3-d_4- and 2,2,3,3,5,6-d_6-piperazine were obtained from a strategically deuterated hydroxyethylenediamine precursor using the same route. In all cases, deuteration of bisoxazolidines proceeded with *trans* stereoselectivity.

Key words: bisoxazolidine, *N,N'*-substituted piperazine, amino alcohols, asymmetric synthesis, condensation, reductions



Scheme 1

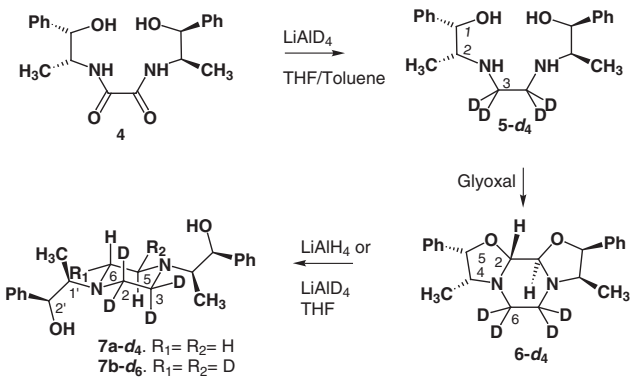
Despite the importance of piperazine-containing molecules owing to their broad spectrum of pharmacological activities[1–4] only a few asymmetric routes for preparing chiral piperazines have been described in the literature which include the syntheses of piperazine carboxylic acids,[5,6] 2-substituted piperazines,[7,8] 2,6-methylated piperazines[9] or benzyl-α-D-arabinopyranoso[3,4-*b*]piperazines,[10] all of which provide optically pure material. As part of our research involving the synthesis and study of heterocyclic compounds,[11–13] we have recently described a new route for the preparation of symmetrical and unsymmetrical piperazines[14] using condensation reactions in which the stereochemical outcome is controlled by the stereochemistry of bisoxazolidine type structures. To our knowledge, there are no reports concerning methodologies for the construction of *N,N'*-substituted piperazines strategically ring labelled with deuterium, therefore, in this paper, the synthesis of piperazine norephedrine derivatives in which the ring methylenes are stereoselectively labelled with deuterium is reported.

Compound **1** was obtained by treatment of (1*S*,2*R*)-(+)-norephedrine with 1,2-dibromoethane in a sealed ampoule at 130 °C. Subsequent condensation of diamine **1** with glyoxal or butanedione led to the formation of previously reported bisoxazolidines **2a** and **2b**. Stereoselective incorporation of deuterium atoms into the 2- and 3-positions of piperazines was accomplished by reduction of **2a** and **2b** using $LiAlD_4$ or BD_3•THF to yield the dideuterated piperazines **3a**-d_2 and **3b**-d_2 with *trans* stereochemistry, as shown in Scheme 1.

Evidence for the formation of these piperazines was obtained from mass spectral and NMR data. The existence of only one diastereoisomer was confirmed by addition of four equivalents of Pirkle's reagent.[15] The ^{1}H NMR spectrum of **3a**-d_2 showed a broad multiplet between 2.71 ppm and 2.57 ppm for the methylene at position 5 and a broad singlet at 2.56 ppm for CHD-2, while the same carbons appeared as a broad singlet at 50.8 ppm in the ^{13}C NMR spectrum. As expected, these molecules show dynamic behavior due to ring inversion and the energy required for this process was obtained by variable temperature ^{13}C NMR experiments. Thus upon cooling to 223 K two singlets corresponding to the diastereotopic carbons at positions 5 and 6 were observed at 52.1 ppm and 49.5 ppm, whereas CD-2 and CD-3 appeared as two broad singlets at 51.7 ppm and 49.1 ppm. The coalescence temperature was achieved at 262 K, and a $\Delta G^{\neq} = 12.2$ kcalmol^{-1} in agreement with the value reported for the non-deuterated analogue, was calculated for the interconversion process using the Eyring equation. In the mass spectrum the $m/z = 357$ ion corresponding to $M^+ + 1$ was detected. The ^{1}H NMR spectrum of piperazine **3b**-d_2 displayed signals for a single isomer and the ring methyl group appeared as a singlet at 1.23 ppm, indicating no coupling to the deuterium atom while the ^{13}C NMR spectrum showed a triplet shifted to 58.4 ppm ($J_{CD} = 20.8$ Hz). Mass spectrometric data revealed the $m/z = 385$ ion corresponding to the $M^+ + 1$ ion.

The same methodology was applied for the preparation of piperazines **7a**-d_4 and **7b**-d_6 (Scheme 2) starting from the previously described[16–18] diamide **4**. Since reduction with $LiAlD_4$ in THF yielded a mixture of diamine **5**-d_4 and starting material, the reaction was carried out in a mixture of refluxing THF/toluene for 48 hours to yield exclusively the diamine **5**-d_4. The ^{1}H NMR spectrum of **5**-d_4 showed no signals for methylene groups and the ^{13}C spectrum showed a quintet shifted to 46.1 ppm ($J_{CD} = 20.0$ Hz). Mass spectrometry showed the $m/z = 334$ and 333 ions corresponding to $M^+ + 2$ and $M^+ + 1$, respectively. Treat-

ment of diamine **5**-d_4 with glyoxal gave bisoxazolidine **6**-d_4 as a single product displaying the signal for C-6 as a quintet at 45.2 ppm (J_{CD} = 20.0 Hz) in the ^{13}C NMR spectrum and the m/z = 355 ion which corresponds to the M^+ + 1 in mass spectrometry.



Scheme 2

The synthesis of piperazines **7a**-d_4 and **7b**-d_6 was achieved by reduction of bisoxazolidine **6**-d_4 using $LiAlH_4$ or $LiAlD_4$, respectively. The stereochemistry of bisoxazolidine **6**-d_4 accounts for the stereochemical outcome of these piperazines. For compound **7a**-d_4, CH_2-5 gives rise to a broad AB system in the ^{1}H NMR which is overlapped with the doublet of quartets for H-1'. Additionally, the ^{13}C NMR spectrum showed two broad signals at 50.9 ppm and 49.1 ppm which correspond to C-5 and CD_2-2, the spin-spin couplings for the deuterated carbon were not observed due to dynamic behavior. For this compound the M^+ ion was absent and the base peak at m/z = 251 corresponding to M^+ + 1 with loss of CHPhOH fragment was detected. The ^{1}H NMR spectrum of piperazine **7b**-d_6 exhibited a broad singlet at 2.58 ppm for CH-5 while CD_2-2 and CDH-5 appeared at 50.5 ppm in the ^{13}C NMR spectrum. Mass spectrometry showed the m/z = 361 ion corresponding to M^+ + 1 and the base peak at m/z = 253 corresponding to M^+ + 1 with loss of CHPhOH fragment as observed for compound **7a**-d_4. Although these compounds also show dynamic behavior, attempts to obtain spectra at low temperature were unsuccessful since they precipitate at 273 K in chloroform or dichloromethane solution.

In conclusion we have completed the stereoselective synthesis of four piperazines strategically deuterated in the ring methylenes based on the reduction of norephedrine derived bisoxazolidines with $LiAlH_4$, $LiAlD_4$ or BD_3•THF and applying the sequence previously described. The synthesis described herein provides easily stereocontrolled access to optically active piperazines in good yield and the new derivatives contain two new stereogenic carbons in the ring labelled with deuterium atoms.

All reagents were purchased from Aldrich. BD_3•THF was prepared from $NaBD_4$ using the procedure described in the literature.[19] ^{1}H and ^{13}C NMR spectra were recorded on a Jeol-270 spectrometer. Chemical shifts (ppm) are relative to TMS. Coupling constants are quoted in Hz. The HETCOR and COSY standard pulse sequence, which incorporates quadrature detection in both domains was used. Infrared spectra were recorded on a Perkin Elmer 16F spectrophotometer. Mass spectra were obtained with a HP 5989A mass spectrometer. Optical rotations were measured on a Perkin Elmer 241 polarimeter, $[\alpha]_D^{25}$ values are given in deg $cm^{-2}g^{-1}$. Melting points were obtained on a Gallenkamp MFB-595 apparatus and are uncorrected.

(1*S*,2*R*)-*N*,*N*'-Bis-[(1-hydroxy-2-methyl-1-phenyl)ethyl]ethylenediamine (1)

A mixture of (+)-norephedrine (5.0 g, 33.0 mmol) and 1,2-dibromoethane (1.42 mL, 16.5 mmol) was heated in a sealed ampoule for 8 h at 100 °C. After cooling, the solid was washed with $CHCl_3$ yielding a white product (4.85 g, 14.3 mmol). Following addition of aq NaOH (1.14 g, 27.74 mmol) the free amine was extracted with $CHCl_3$ (3 × 10 mL) to give hydroxyethylenediamine **1** (3.8 g, 70%).

(1'*R*,2'*S*,2*R*,3*R*)-1,4-Bis-[(2'-hydroxy-1'-methyl-2'-phenyl)ethyl]-2,3-d_2-piperazine (3a-d_2)

To a solution of bisoxazolidine **2a** (1.0 g, 2.85 mmol) in anhyd THF (30 mL) was added $LiAlD_4$ (0.47 g, 11.2 mmol) at 0 °C and the mixture was refluxed for 5 h. After cooling, H_2O (10 mL) was added and the suspension was filtered through Celite, dried (Na_2SO_4) and evaporated under reduced pressure to give **3a**-d_2 as a white solid (0.8 g, 80%); mp 164–165 °C; $[\alpha]_D^{25}$ +3.66 (c = 0.099, CH_2Cl_2).

MS (EI): m/z (%) = 357 (M^+ + 1, 1), 251 (2), 50 (19), 249 (100), 141 (12), 115 (11), 114 (11), 113 (11), 86 (10), 85 (12), 77 (11), 57 (25), 56 (14), 43 (19), 42 (11), 29 (10).

IR (KBr): ν = 3400, 3086, 3064, 3030, 3004, 2984, 2962, 2928, 2916, 2900, 2878, 2850, 2830, 2706, 1492, 1452, 1396, 1352, 1170, 1154, 1128, 1034, 756, 736, 720, 700 cm^{-1}.

^{1}H NMR (270.17 MHz, $CDCl_3$): δ = 7.36–7.22 (5 H, m, H-*o*,*p*,*m*), 4.89 (1 H, d, J = 3.7 Hz, H-2'), 2.71–2.57 (3 H, m, H-1', CH_2-5), 2.56 (1 H, br s, CHD-2), 0.82 (3 H, d, J = 6.9 Hz, CH_3-7).

^{13}C NMR (67.94 MHz, $CDCl_3$): δ = 142.0 (C-*i*), 128.1 (C-*o*), 126.9 (C-*p*), 126.0 (C-*m*), 71.9 (C-2'), 64.3 (C-1'), 50.8 (br s, CH_2-5, CHD-2), 10.3 (C-7).

(2'*S*,1'*R*,2*S*,3*S*)-1,4-Bis-[(2'-hydroxy-1'-methyl-2'-phenyl)ethyl]-2,3-dimethylpiperazine-2,3-d_2 (3b-d_2)

To a solution of bisoxazolidine **2b** (0.70 g, 1.85 mmol) in anhyd THF (30 mL) was added BD_3•THF (14.8 mL, 0.5 M) at 0 °C and the mixture was refluxed for 5 h. After cooling, H_2O (20 mL) was added and the solvent evaporated with a Dean-Stark trap. The organic phase was extracted with $CHCl_3$ (3 × 10 mL) and the solvent was evaporated under reduced pressure to give **3b**-d_2 (0.68 g, 95%) as a white solid; mp 110–111 °C; $[\alpha]_D^{25}$ +58.027 (c = 0.301, $CHCl_3$).

MS (EI): m/z (%) = 385 (M^+ + 1,1), 278 (27), 276 (4), 171 (5), 155 (14), 107 (5), 99 (6), 79 (10), 43 (8).

IR (KBr): ν = 3438, 3024, 2984, 2974, 2958, 2918, 2848, 2364, 2344, 1472, 1464, 1458, 1450, 1382, 1358, 1198, 1176, 1164, 1108, 1100, 1064, 1006, 974, 748, 744, 696, 668 cm^{-1}.

^{1}H NMR (270.17 MHz, $CDCl_3$): δ = 7.34–7.18 (5 H, m, arom), 4.66 (1 H, d, J = 4.5 Hz, H-2'), 2.92 (1 H, dq, J = 4.5, 6.9 Hz, H-1'), 2.65 and 2.17 (2 H, AB, J = 7.6 Hz, H-5), 1.23 (3 H, s, CH_3-7), 0.85 (3 H, d, J = 6.9 Hz, CH_3-8).

^{13}C NMR (67.94 MHz, $CDCl_3$): δ = 141.8 (C-*i*), 128.0 (C-*o*), 127.0 (C-*p*), 126.2 (C-*m*), 73.2 (C-2'), 60.5 (C-1'), 58.4 (t, J_{CD} = 20.8 Hz, C-2), 41.7 (C-5), 12.4 (C-8), 11.5 (C-7).

(1*S*,2*R*)-*N,N'*-Bis-[(1-hydroxy-2-methyl-1-phenyl)ethyl]ethylene-d_4-diamine (5-d_4)

To a solution of diamide **4**[16–18] (1.0 g, 2.8 mmol) in a mixture of anhyd THF (15 mL) and anhyd toluene (20 mL) was added $LiAlD_4$ (0.47 g, 11.2 mmol) at 0 °C and the mixture was refluxed for 48 h. After cooling, H_2O (10 mL) was added and the solution was filtered through Celite, dried (Na_2SO_4) and evaporated under reduced pressure to afford **5**-d_4 (0.91 g, 97%) as a white solid; mp 91–92 °C; $[\alpha]_D^{25}$ –4.03 (*c* = 0.322, CH_2Cl_2).

MS (EI): *m/z* (%) = 334 (M^+ + 2, 2), 333 (M^+ + 1, 6), 226 (21), 225 (100), 207 (40), 164 (24), 148 (19), 117 (10), 107 (29), 91 (10), 79 (28), 77 (24), 76 (16), 74 (12), 60 (22), 47 (14), 44 (10), 42 (10), 32 (11).

IR (KBr): ν = 3150, 3086, 3068 3026, 2968, 2908, 2850, 1492, 1452, 1422, 1406, 1374, 1138, 1084, 1010, 1000, 942, 760, 708, 698, 550 cm^{-1}.

^{1}H NMR (270.17 MHz, $CDCl_3$): δ = 7.36–7.20 (5 H, m, H-*o*,*m*,*p*), 4.69 (1 H, d, *J* = 4.0 Hz, H-1), 2.88 (1 H, dq, *J* = 4.0, 6.4 Hz, H-2), 0.84 (3 H, d, *J* = 6.4 Hz, CH_3-4).

^{13}C NMR (67.94 MHz, $CDCl_3$): δ = 141.6 (C-*i*), 128.2 (C-*o*), 127.2 (C-*p*), 126.2 (C-*m*), 76.6 (C-1), 58.5 (C-2), 46.1 (quint, J_{CD} = 20.0 Hz, CD_2-3), 14.9 (C-4).

(5*S*,5'*S*,4*R*,4'*R*,2*R*,2'*R*)-*N,N'*-Ethylene-d_4-[(4,4'-dimethyl-5,5'-diphenyl)]-2,2'-bisoxazolidine (6-d_4)

A solution of diamine **5**-d_4 (0.91 g, 2.74 mmol) in EtOH (40 mL) and aq glyoxal (0.39 mL, 40%) was refluxed for 12 h. After cooling, the solvent was removed under reduced pressure to afford **6**-d_4 (0.68 g, 70%) as a white solid; mp 194–195 °C; $[\alpha]_D^{25}$ –48.48 (*c* = 0.099, CH_2Cl_2).

MS (EI): *m/z* (%) = 356 (M^+ + 2, 5), 355(M^+ + 1, 13), 354 (M^+, 10), 353 (10), 326 (21), 235 (38), 208 (13), 207 (33), 148 (22), 135 (15), 134 (10), 130 (25), 119 (16), 118 (100), 105 (14), 101 (14), 91 (36), 78 (10), 77 (15), 54 (15).

IR (KBr): ν = 2894, 2810, 1452, 1284, 1234, 1224, 1192, 1128, 1114, 1098, 1090, 986, 978, 748, 738, 708 cm^{-1}.

^{1}H NMR (270.17 MHz, $CDCl_3$): δ = 7.35 (2 H, d, *J* = 7.7 Hz, H-*o*), 7.32 (2 H, t, *J* = 7.7 Hz, H-*m*), 7.26 (1 H, t, *J* = 7.7 Hz, H-*p*), 5.14 (1 H, d, *J* = 7.7 Hz, H-5), 4.00 (1 H, s, H-2), 3.07 (1 H, dq, *J* = 6.2, 7.7 Hz, H-4), 0.70 (3 H, d, *J* = 6.2 Hz, CH_3-7).

^{13}C NMR (67.94 MHz, $CDCl_3$): δ = 139.7 (C-*i*), 127.9 (C-*o*), 127.7 (C-*m*), 127.6 (C-*p*), 93.8 (C-2), 83.2 (C-5), 60.0 (C-4), 45.2 (quint, J_{CD} = 20.0 Hz, CD_2), 14.3 (C-7).

(2'*S*,1'*R*)-1,4-Bis-[(2'-hydroxy-1'-methyl-2'-phenyl)ethyl]-2,2,3,3-d_4-piperazine (7a-d_4)

To a solution of bisoxazolidine **6**-d_4 (0.18 g, 0.508 mmol) in anhyd THF (30 mL) was added $LiAlH_4$ (0.077 g, 2.03 mmol) and the mixture was refluxed for 5 h. After cooling, H_2O (10 mL) was added and the solution was filtered through Celite, dried (Na_2SO_4) and evaporated under reduced pressure to afford **7a**-d_4 (0.130 g, 72%) as a white solid; mp 164–165 °C; $[\alpha]_D^{25}$ –0.45 (*c* = 0.297, CH_2Cl_2).

MS (EI): *m/z* (%) = 253 (4), 252 (21), 251 (100), 117 (15), 116 (14), 115 (14), 88 (12), 86 (18), 79 (13), 77 (13), 74 (11), 59 (10), 58 (18), 56 (13).

IR (KBr): ν = 3402, 3062, 2928, 2850, 998, 932, 752, 710, 700, 550 cm^{-1}.

^{1}H NMR (270.17 MHz, $CDCl_3$): δ = 7.35–7.24 (5 H, m, H-*o*,*m*,*p*), 4.91 (1 H, d, *J* = 4.0 Hz, H-2'), 2.69 (1 H, dq, *J* = 4.0, 7.0 Hz, H-1'), 2.70–2.61 (2 H, br AB, CH_2-5), 0.84 (3 H, d, *J* = 7.0 Hz, CH_3-7).

^{13}C NMR (67.94 MHz, $CDCl_3$): δ = 141.9 (C-*i*), 128.0 (C-*o*), 126.9 (C-*p*), 125.9 (C-*m*), 71.9 (C-2'), 64.3 (C-1'), 50.9 (C-5), 49.9 (br s, CD_2-2), 10.2 (C-7).

(2'*S*,1'*R*,5*R*,6*R*)-1,4-Bis-[(2'-hydroxy-1'-methyl-2'-phenyl)ethyl]-2,2,3,3,5,6-d_6-piperazine (7b-d_6)

To a solution of bisoxazolidine **6**-d_4 (0.45 g, 1.27 mmol) in anhyd THF (30 mL) was added $LiAlH_4$ (0.21 g, 5.08 mmol) at 0 °C and the mixture was refluxed for 5 h. After cooling, H_2O (10 mL) was added, the suspension filtered through Celite, dried (Na_2SO_4) and evaporated under reduced pressure to yield the piperazine **7b**-d_6 (0.321 g, 70%) as a white solid; mp 168–170 °C; $[\alpha]_D^{25}$ +8.08 (*c* = 0.099, CH_2Cl_2).

MS (EI): *m/z* (%) = 361 (M^+ + 1, 1), 265 (3), 254 (22), 253 (100), 119 (8), 118 (9), 117 (8), 89 (10), 88 (12), 77 (20), 60 (11), 58 (15), 57 (12).

IR (KBr): ν = 3400, 2960, 2916, 2900, 1012, 976, 748, 706, 700, cm^{-1}.

^{1}H NMR (270.17 MHz, $CDCl_3$): δ = 7.35–7.22 (5 H, m, H-*o*,*p*,*m*), 4.91 (1 H, d, *J* = 3.7 Hz, H-2'), 2.68 (1 H, dq, *J* = 3.7, 7.0 Hz, H-1'), 2.58 (1 H, br s, CHD-5), 0.83 (3 H, d, *J* = 7.0 Hz, CH_3-7).

^{13}C NMR (67.94 MHz, $CDCl_3$) δ = 141.9 (C-*i*), 128.0 (C-*o*), 126.9 (C-*p*), 125.9 (C-*m*), 71.9 (C-2'), 64.3 (C-1'), 50.5 (br, CHD-5, CD_2-2), 10.2 (C-7).

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References

(1) Giardinà, D.; Gulini, U.; Massi, M.; Piloni, M. G.; Pompei, P.; Rafaiani, G.; Melchiorre, C. *J. Med. Chem.* **1993**, *36*, 690.
(2) Bøgesø, K. P.; Arnt, J.; Frederiksen, K.; Hansen, H. O.; Hyttel, J.; Pedersen, H. *J. Med. Chem.* **1995**, *38*, 4380.
(3) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I. W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, *37*, 3443.
(4) Katsura, Y.; Zhang, X.; Homma, K.; Rice, K.C.; Calderon, S. N.; Rothman, R. B.; Yamamura, H. I.; Davis, P.; Flippen-Anderson, J. L.; Xu, H.; Becketts, K.; Foltz, E. J.; Porreca, F. *J. Med. Chem.* **1997**, *40*, 2936.
(5) Warshawsky, A. M.; Patel, M. V.; Cheng, T. M. *J. Org. Chem.* **1997**, *62*, 6439.
(6) Schanen, V.; Cherrier, M. P.; de Melo, S. J.; Quirion, J. C.; Husson, H. P. *Synthesis* **1996**, *7*, 833.
(7) Schanen, V.; Riche, C.; Chiaroni, A.; Quirion, J. C.; Husson, H. P. *Tetrahedron Lett.* **1994**, *35*, 2533.
(8) Soukara, S.; Wünsch, B. *Synthesis* **1999**, *10*, 1739.
(9) Mickelson, J. W.; Belonga, K. L.; Jacobsen, E. J. *J. Org. Chem.* **1995**, *60*, 4177.
(10) Abdel-Jalil, R. J.; Al-Qawasmeh, R. A.; Al-abed, Y.; Voelter, W. *Tetrahedron Lett.* **1998**, *39*, 7703.
(11) Santes, V.; Ortiz, A.; Santillan, R.; Gutiérrez, A.; Farfán, N. *Synth.Commun.* **1999**, *29*, 1277.
(12) Santes, V.; Gómez, E.; Jiménez, G.; Santillan, R.; Gutiérrez, A.; Farfán, N. *Synth.Commun.* **2000**, *30*, 2721.

(13) Santes, V.; Rojas-Lima, S.; Santillan, R. L.; Farfán, N. *Monatsh. Chem.* **1999**, *130*, 1481.
(14) Ortíz, A.; Farfán, N.; Höpfl, H.; Santillan, R.; Ochoa, M. E.; Gutiérrez, A. *Tetrahedron: Asymmetry* **1999**, *10*, 799.
(15) Pirkle, W. H.; Hoover, D.; *Topics in Stereochemistry*; John Wiley and sons: New York, 1982; vol 13, p 263.
(16) Martínez-Martínez, F. J.; Ariza-Castolo, A.; Tlahuext, H.; Tlahuextl, M.; Contreras, R. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1481.
(17) Martínez-Martínez, F. J.; Padilla-Martínez, I. I.; Brito, M. A.; Geniz, E. D.; Rojas, R. C.; Saavedra, J. B. R.; Höpfl, H.; Tlahuextl, M.; Contreras, R. *J. Chem. Soc., Perkin Trans. 2* **1998**, 401.
(18) Flores-Parra, A.; Suárez-Moreno, P.; Sánchez-Ruíz, S. A.; Tlahuextl, M.; Jaen-Gaspar, J.; Tlahuext, H.; Salas-Coronado, R.; Cruz, A.; Nöth, H.; Contreras, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1661.
(19) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley: New York, 1975; p 18.

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